REMARKS

Applicants acknowledge that on page 3 of the Office Action of July 17, 2002, the Examiner has requested cancellation of claims 27-32 in accordance with MPEP § 821.01. Applicants point out that claims 27-32 are method claims which rely on the product of claim 1. Therefore, upon allowance of claim 1, it is believed that claims 27-32 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)." Applicants believe that claim 1 is now in condition for allowance and therefore believe that rejoinder of claims 27-32 is appropriate.

Amendments

Claim 1 has been amended to include instruction as to how to compare "variants" of SEQ ID NO:1. To expedite prosecution, Applicants have amended Claim 1 b) as suggested by the Examiner to include making a comparison of variants along the entire length of SEQ ID NO:1. Claim 1 b) has been amended to read, "a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1 over the entire length of SEQ ID NO:1." Support for this amendment may be found throughout the specification, for example, page 11, line 6-8 in which SEQ ID NO:1 is identified as being 253 amino acids in length, thereby identifying the entire length of SEQ ID NO:1 as 253 amino acid residues. Applicants respectfully request entry of the amendment to expedite prosecution or to further simplify matters for appeal.

Utility rejections under 35 U.S.C. § 101 and § 112

The rejections of claims 1, 18-20, 25 and 26 are improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue, identified in the patent application as a novel human prostate-associated kallikrein protein, abbreviated as HPAK, is a polypeptide sequence encoded by a gene that is expressed in humans. The novel polypeptide is demonstrated in the specification and in subsequent analyses *infra* to be a member of the serine protease family and kallikrein subfamily

(Specification, p. 1, lines 7-8; p. 11, lines 6-12). As such, the claimed invention has numerous practical, beneficial uses in the diagnosis of acquired and inherited disease, expression profiling, and drug development, none of which require knowledge of how the polypeptide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants' invention comprises, *inter alia*, a novel human prostate-associated kallikrein protein (hereinafter referred to as HPAK) and naturally-occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO:1 over the entire length of SEQ ID NO:1. HPAK, and variants thereof, are useful in the diagnosis of acquired and inherited disease, expression profiling, and drug development. HPAK shares chemical and structural homology with human pancreatic kallikrein (GI 186653). In particular, HPAK shares 54% identity with GI 186653, including the conserved amino acid residues for serine protease activity, H_{65} D_{113}, and S_{206}. Also conserved are 10 cysteine residues (31, 50, 66, 145, 166, 177, 191, 202. 212, and 227; see Figure 2) which are structurally important and involved in the formation of five disulfide bonds, as well as D_{200}, which likely confers chymotrypsinogen-like activity on HPAK. The similar hydrophobicity plots of HPAK and GI 186653 (Figures 3 and 4) indicate that these molecules have a similar structure.

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. HPAK is, in that regard, homologous to human pancreatic kallikrein, a protein having both serine protease activity and kallikrein-like cleavage specificity. In particular, the two polypeptides share more than 52 % sequence identity over 253 amino acid residues. HPAK and human pancreatic kallikrein also share similar amino terminal signal sequences, hydrophobicity plots and conserved residues for serine protease activity, H_{65}, D_{113}, and S_{206} (Figures 2, 3 and 4). Additional evidence of the similarity of HPAK (SEQ ID NO:1) to human kallikrein proteins is found in section II. *infra.*

This is more than enough homology to demonstrate a reasonable probability that the utility of human pancreatic kallikrein can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998). Given homology in excess of 40% over many more than 70 amino acid

residues, the probability that the claimed polypeptide is related to human pancreatic kallikrein is, accordingly, very high.

There is, in addition, direct proof of the utility of the claimed invention. Applicants have submitted the Declaration of Lars Michael Furness[1] describing some of the practical uses of the claimed invention. These uses include gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 11).

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

Applicants maintain the arguments set forth in the response submitted April 26, 2002 (paper No. 17), pages 7-8.

[1] The Furness Declaration was originally submitted in unexecuted form, the executed form having been signed April 30, 2002 and submitted on August 1, 2002. Therefore, Applicants believe consideration of the executed Furness Declaration is proper and should receive full consideration.

II. Use of the claimed polypeptides for diagnosis of conditions or diseases characterized by expression of HPAK, for the diagnosis of acquired and inherited disease, expression profiling, and drug development, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

Applicants maintain the arguments set forth in the response submitted April 26, 2002 (paper No. 17), pages 9-14. Additionally, Applicants are hereby submitting further evidence supporting Applicants position that SEQ ID NO:1 is a member of the kallikrein protein family. This evidence is the result of scientific discoveries made subsequent to January 29, 1997, the filing date of the parent application to which priority is claimed.

First, the Office Action asserts that "SEQ ID NO:1 has not been shown to be functionally related to a human pancreatic kallikrein" (Office Action of July 17, 2002, p. 6). Applicants respectfully bring to the Examiner's attention that SEQ ID NO:1 is a human prostate kallikrein (see the Specification, p. 2, lines 11-13). In addition to the amino acid sequence alignment of SEQ ID NO:1 to human kallikreins as shown in Figure 2, Applicants have conducted a BLASTP search of SEQ ID NO:1 against the Genpept database (NCBI, version 131, Exhibit A). What is immediately evident is the **90% overall sequence identity** of SEQ ID NO:1 with numerous human kallikrein polypeptides such as kallikrein 11 (also known as hippostasin, PRSS20, KLK11, and TLSP) (for example, g18314498, Exhibit B). The BLAST probability score is 1.0e-135, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. The results of BLASTP analysis provides clear and convincing evidence that SEQ ID NO:1 is a member of the kallikrein protein family.

Secondly, the Office Action alleges that "neither the specification, nor the art of record teaches any association of SEQ ID NO:1 with a protease or chymotrypsinogen activity" (Office Action of July 17, 2002, p. 6). Contrary to this allegation, Applicants maintain that residues H_{65}, D_{113}, and S_{206} are important for serine protease activity, and that residue D_{200} likely confers chrymotrypsinogen-like activity to SEQ ID NO:1. In further support of the protease or chymotrysinogen activity of SEQ ID NO:1, Applicants submit herewith the results of an evaluation of the conserved domains within g18314498, human kallikrein 11, which has 90% sequence identity to SEQ ID NO:1 (Exhibit C). What is readily evident is that both the trypsin-like serine protease and trypsin domains within human kallikren 11 are **also present** within SEQ ID NO:1 (compare the region of 100% sequence identity between SEQ ID NO:1 and g18314498 in Exhibit A (L61-N253) with the trypsin-like serine protease and trypsin domains of g18314498,

R24-I254 in Exhibit C). The Office Action has asserted that there is no indication that H_{65}, D_{113}, and S_{206}, three non-contiguous conserved amino acids and D_{200} are important for serine protease activity. Clearly, not only are these four amino acids present within the trypsin-like serine protease and trypsin domains, SEQ ID NO:1 has 100% amino acid sequence identity with human kallikren 11 at these domains. The similarity of SEQ ID NO:1 to human kallikrein 11 provides further evidence that SEQ ID NO:1 would be expected by one of skill in the art to have serine protease activity.

Thirdly, although the Office Action of July 17, 2002 concedes that SEQ ID NO:1 has 10 conserved cysteine residues which are involved in the formation of five disulfide bonds, the Office Action provides no reasoning or scientific basis for its conclusion that "there is no indication that these cysteines would form disulfide bonds in SEQ ID NO:1. Perhaps the Office is confused with this line of reasoning. Applicants bring to the Examiner's attention that SEQ ID NO:1 is also 90% identical to g10799396, *Homo sapiens* kallikrein 11 (see Exhibit A). When the "B-Link" hyperlink under the "Links" hyperlink is selected in g10799396, a list of Matching gi numbers (i.e., those gi numbers identical to g10799396) is displayed (Exhibit D) which includes g1834498 and Swiss-Prot entry g9296987. Examination of g9296987 (Exhibit E) and the annotation associated with this 250 amino acid long human kallikrein 11 precursor protein indicates the following structural characteristics:

1. a potential signal peptide, M1-G18,
2. six disulfide bonds between residues: (28, 163), (47, 63), (135, 237), (142, 209), (174, 188), and (199, 224).

Moreover, g9296987 is functionally annotated as a "possible multifunctional protease and is a "secreted" protein, belonging to the peptidase family S1 and the Kallikrein subfamily.

Because SEQ ID NO:1 shares sequence identity with g9296987 within the disulfide bonds identified, one of ordinary skill in the art would be more likely than not to conclude that SEQ ID NO:1 <u>also</u> forms disulfide bonds, similarly functions as a protease and is a member of the kallikrein family.

Fourth, the Office Action further doubts the expression of SEQ ID NO:1 or its association with various cancers, because SEQ ID NO:1 is a "deduced" amino acid sequence encoded by SEQ ID NO:2. Furthermore, the Office Action asserts that it is "unpredictable that the claimed polypeptide of SEQ ID NO:1 is expressed in cancer tissue in nature and/or overexpressed in

cancer tissues as compared to normal tissues (Office Action of July 17, 2002, pp. 8 and 13). Applicants respectfully bring to the Examiner's attention the annotation associated with g10799396, in which the expression of kallikrein 11 is found in brain, skin (isoform 1 is preferentially expressed in the brain) and prostate (isoform 2 is preferentially expressed in the prostate). These expression patterns have been independently substantiated by other investigators.

Yousef, G.M. et al. have also identified isoform 1 in brain and skin tissues (Yousef, G.M. et al. (2000) Genomics 63:88-96, g5713131, Exhibit F, enclosed herewith). Mitsui, S. et al. in Kyoto Japan have also identified isoform 2 in prostate tissue (Mitsui,S. et al., (2000) Biochem. Biophys. Res. Commun. 272:205-211, and g8574439, Exhibit G, enclosed herewith). Furthermore, Yousef,G.M. et al. have demonstrated that kallikrein 11 (TLSP) is up-regulated by both estrogens and glucocorticoids (p. 93). Additionally, Nakamura, T. et al. have found that all prostate cancer cell lines tested expressed only isoform 1 and not isoform 2, while both normal prostate and benign prostatic hypertrophy (BPH) tissues expressed both isoforms. Nakamura, T. et al. conclude that kallikrein 11 (hippostasin) may be used as a marker to distinguish prostate cancer and BPH (Nakamura, T. et al. (2001) Prostate 49:72-78, Exhibit H). The identification, isolation and expression of kallikrein 11 by numerous investigators in addition to Applicants own findings provide further substantial, credible and convincing evidence that not only is SEQ ID NO:1 expressed, but that it is more likely than not yet another novel kallikrein expressed predominantly in prostate tissues as indicated in Figure 5 of the instant specification.

One of ordinary skill in the art would be more likely than not to conclude that as with human kallikrein11, a kallikrein known to have serine protease activity, SEQ ID NO:1 would also have serine protease activity as demonstrated by i.) its homology to kallikrein 11, ii.) the presence in SEQ ID NO:1 of amino acid residues H_{65}, D_{113}, and S_{206}, and D_{200}, known to be essential for serine protease activity, and as described byYousef, G.M. et al. pp. 91-92 (Exhibit F), iii.) the structure and 3-dimensional structure of SEQ ID NO:1 as disclosed in the Swiss-Prot entry for g9296987, submitted in Exhibit E, and iv) the expression profile of SEQ ID NO:1 as presented in Figure 5. Taken together, these data support the strong likelihood of SEQ ID NO:1 being a novel member of the kallikrein subfamily of serine proteases.

Lastly, the Office Action provides no evidence that secretion is not a serine protease activity. Again, it appears the Office has confused activity and the property/structural

characteristic of a protein. Serine proteases are themselves secreted proteins (see for example, Olsson, A.Y. et al., DNA Cell Biol. (2000) 19:721-727, enclosed herewith, Exhibit I), secretion is a property of a serine protease, not an activity of a serine protease. The Examiner must accept the Applicants' demonstration that the homology between the claimed invention and human kallikrein 11 demonstrates utility beyond a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

The teachings of Bowie et al., Lazar et al., Burgess et al., and Bork are not applicable for reasons argued by Applicants in paper No. 17 and further, based on the evidence presented as to the 90% sequence homology to human kallikrein 11, the presence of trypsin and serine protease domains and further analysis of the 3-dimensional structure of kallikrein 11 which can be extrapolated to SEQ ID NO:1. SEQ ID NO:1 is most certainly not only a member of the kallikrein gene family, but a member of the serine protease family of enzymes. The importance and utility of SEQ ID NO:1 as a serine protease enzyme and its use in the diagnosis of acquired and inherited disease, expression profiling, and drug development can and is understood by one of skill in the art, unequivocally.

B. The uses of HPAK for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Furness Declaration, the substance of which must be considered by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application is a divisional of, and claims priority to, U.S. Ser. No. 08/790,137, filed January 29, 1997, having the identical Specification, (hereinafter "the Hillman '137 application").

The Office Action doubts the expression of SEQ ID NO:1, as SEQ ID NO:1 is a "deduced" amino acid sequence for the polynucleotide sequence of SEQ ID NO:2. Clearly, as

the results of the Genpept 131 BLASTP analysis show (Exhibit A), not only is SEQ ID NO:1 expressed, it has been identified by numerous separate groups further supporting the expression of SEQ ID NO:1 and its utility in both two-dimensional gel electrophoresis and Western blot analysis to monitor protein expression and assess drug toxicity. These utilities are available as suggested by the tissue specific expression of SEQ ID NO:2 encoding SEQ ID NO:1 in both pancreas and prostate tissues. Supporting references include: Gan,L. et al., (2000) Gene 257:119-130, abstract only, Exhibit J and Yousef, G.M. et al., (2001) 22:184-204, Exhibit K, both enclosed herewith. Therefore, for at least the above reasons, Applicants believe withdrawal of the rejection under 35 U.S.C. § 101 is proper.

Written description rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 20, 25 and 26 stand rejected under 35 U.S.C. § 112, first paragraph, alleged lack of an adequate written description. This rejection is respectfully traversed.

The arguments presented in the response filed April 9, 2001 are reiterated herein. The Office Action asserts that the "numerous claimed variants" are not defined in terms of chemical structure. This position, however, ignores the recitation of "SEQ ID NO:1" as a basis for defining the claimed naturally-occurring variants. Moreover, this position ignores the Brenner et al. document ("Assessing sequence comparisons methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; of record), which reports that through exhaustive analysis of a dataset of proteins with known structural and functional relationships and with <90% overall sequence identity, 30% identity has been determined to be a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. The "90% variants" claimed in the subject application are clearly of much less variation that the available threshold.

Furthermore, the Office Action asserts that ". . . the scope of the claims includes numerous structural variants. No common structural attributes that identify the claimed variants are disclosed, because the function of SEQ ID NO:1 is not known." However, as discussed above in connection with the utility rejection, ample evidence has been presented which establishes that SEQ ID NO:1 is a kallikrein and the presence of the serine protease and chymotrypsin domains, domains indicative and characteristic of serine protease activity, and further substantiating Applicants position that SEQ ID NO:1 is a serine protease. Additionally,

Brenner et al. indicate that polypeptides having 90% sequence similarity would be expected to function similarly. Applicants have described the shared properties (protease domains) and characteristics (disulfide bonds and conserved amino acid residues known to be necessary for protease activity) of variants of SEQ ID NO:1, thereby definitively identifying said 90% variants to SEQ ID NO:1.

For at least the above reasons, withdrawal of the written description rejection is requested.

Enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 20, 25 and 26 were also rejected under the first paragraph of 35 U.S.C. §112 because the Specification allegedly is not enabled due to a lack of a well established utility for SEQ ID NO:1. This rejection is traversed. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Scope rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 20, 25 and 26 were also rejected under the first paragraph of 35 U.S.C. §112 because the Specification allegedly does not describe how to make and use the claimed variants of SEQ ID NO:1. This rejection is traversed.

As explained in the response filed April 9, 2001, the claims recite not only that the polypeptides have at least 90% sequence identity to SEQ ID NO:1, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of HPAK) and SEQ ID NO:2 (the polynucleotide sequence of HPAK), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 over the entire length of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the

Specification of the instant application. See, *e.g.*, page 33, lines 10-22; and Example VI at page 43. Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited variants of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited variants of SEQ ID NO:1, and this rejection should be withdrawn.

Prior art rejections

Claims 1 and 25 stand rejected under 35 U.S.C. 102(b) as being anticipated by Fukushima, D. et al, (GenBank Accession No. A24696). These rejections are traversed.

According to the Office Action, the Fukushima document is pertinent to "90% variants" of SEQ ID NO:1. To expedite prosecution, Applicants have amended Claim 1 b) as suggested by the Examiner to include making a comparison of variants along the entire length of SEQ ID NO:1. Claim 1 b) has been amended and now reads, "a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1 over the entire length of SEQ ID NO:1." Fukushima et al. does not describe such an amino acid sequence. Withdrawal of this rejection is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**, as set forth in the enclosed fee transmittal letter.

Respectfully submitted,

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